CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213793Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	John Sharretts, M.D.
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA 213793
Applicant	Rhythm Pharmaceuticals, Inc.
Date of Submission	March 27, 2020
PDUFA Goal Date	November 27, 2020
Proprietary Name	IMCIVREE
Established or Proper Name	Setmelanotide (RM-493, formerly BIM-22493)
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (POMC), including PCSK1, deficiency obesity or leptin receptor (LEPR) deficiency obesity
Action or Recommended Action:	*Approval*
Approved/Recommended Indication(s)/Population(s) (if applicable)	for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**Ovidiu Galescu, M.D.**
Statistical Review	**Jiwei He, Ph.D.**
Pharmacology Toxicology Review	**Shaji Theodore, MVSc., Ph.D.**
OPQ Review	**Muthukumar Ramaswamy, Ph.D., Joseph Leginus, Ph.D., Theodore Carver, Ph.D., Kumar Janoria, Ph.D.**
Microbiology Review	**Yan Zheng, Ph.D.**
OBP Consult Review	**Ian McWilliams, Ph.D.**
Clinical Pharmacology Review	**Suryanarayana Sista, Ph.D., Eliford Kitabi, Ph.D., Katarzyna Drozda, PharmD, M.S.**
COA Consult Review	**Yasmin Choudhry, M.D.**
DPMH Consult Review	**Jacquline Yancy, Ph.D.,**

OPDP	**Meena Savani, Pharm.D.**
OSI	**Cynthia F. Kleppinger, M.D.**
IRT Consult Review	**Christine Garnett, Pharm.D.**
OSE/DRM	**Mei-Yean Chen, Pharm.D.**
DMEPA	**Melina Fanari, R.Ph.**
DMPP	**Nyedra W. Booker, Pharm.D., MPH**

OBP=Office of Biotechnology Products
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
COA=Clinical Outcomes Assessment
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
DRM=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Imcivree (setmelanotide) is a subcutaneous injection formulation of setmelanotide, a peptide agonist to the human melanocortin-4 receptor (MC4R). The melanocortins are a family of hormones derived from pro-opiomelanocortin (POMC) that regulate energy homeostasis, hunger, and body weight, and include α-melanocyte-stimulating hormone (α-MSH), the endogenous ligand for the MC4R. Leptin regulates hunger, satiety, energy expenditure, and body weight partly via the leptin receptor (LEPR) expressed on POMC neurons in the hypothalamus. Proprotein convertase subtilisin/kexin type 1 (PCSK1) is a protease involved in processing pro-peptides, including POMC.

POMC deficiency, PCSK1 deficiency, and LEPR deficiency are caused by loss-of-function mutations in the *POMC*, *PCSK1*, and *LEPR* genes, respectively. These disorders cause hyperphagia and early onset obesity due to reduced or absent α-MSH signaling at MC4R. Currently, there is no approved treatment for POMC, PCSK1, or LEPR deficiency.

The submission consisted of two nearly identically designed phase 3 studies conducted in two populations. Study RM-493-012 (Study 012) enrolled patients with severe obesity phenotype and biallelic, homozygous, or compound heterozygous loss-of-function mutations in the POMC or PCSK1 genes. Study RM-493-012 (Study 015) enrolled patients with severe obesity phenotype and biallelic, homozygous, or compound heterozygous loss-of-function mutations in the LEPR gene. Both studies were single-arm, open-label, 1-year studies. After dose titration and 10 weeks of open-label treatment, patients who achieved at least a 5-kg weight loss (or at least 5% if baseline body weight <100 kg) entered a double-blind period, consisting of 4 weeks on active treatment and 4 weeks of placebo. After the double-blind period, patients resumed open-label treatment.

The application provides substantial evidence of effectiveness of weight loss in the intended population. In the primary analysis, 80% of patients with POMC or PCSK1 deficiency in Study 012 and 45% of patients with LEPR deficiency in Study 015 achieved ≥10% weight loss from baseline at 1 year. The 95% confidence intervals excluded a historical control responder rate of 5%. There were no missing data in Study 012, and sensitivity analyses of Study 015 did not alter the conclusions. We consider 10% weight loss to constitute a clinically meaningful effect for these patients.

Despite the open-label design of the studies and use of external controls, the observed effect sizes were striking for these rare genetic conditions, where the natural history of progressive weight gain is well-characterized and quite predictable. Weight loss of the magnitude experienced by these patients, and sustained for a year, would be highly unlikely to occur in the absence of pharmacologic treatment. Even in a general (non-syndromic) obese and overweight population, results of this magnitude would be highly unusual in the absence of treatment. For example, in clinical trials of weight-loss products to support registration for a weight management indication, patients assigned to placebo (on a background standard-of-care diet and exercise program) experienced

mean weight loss of 1.2% to 2.5% at one year.[1]

The key secondary weight-loss endpoint also achieved statistical significance at an alpha level of 0.05. Mean Percent Change in weight from baseline to 1 year was -23.1% in Study 012 and -9.7% in Study 015. The double-blind withdrawal period provided supportive evidence of the effect of setmelanotide on weight loss in the study populations, as it allowed each subject to serve as his or her own control. In both studies, patients experienced an increase in body weight with double-blind withdrawal of study drug, and a decrease in weight after the study drug was resumed.

Results for the secondary hunger endpoints do not provide substantial evidence of effectiveness, although the data are suggestive of a salutary effect. Given the subjectivity of the endpoint, the open-label study was unable to distinguish the treatment effect from expectation bias and outside influences. Moreover, missing data, the absence of a historical control, and limitations of the PRO instrument limit estimation of a clinically meaningful treatment effect. Nevertheless, the double-blind, placebo withdrawal data suggest that setmelanotide reduces hunger in some patients with POMC, PCSK1, and LEPR. Some patients whose hunger scores improved during open-label treatment experienced worsening hunger scores during the double-blind placebo period, which improved when study drug resumed. Hunger results were highly variable, however, and not always consistent with weight loss. Changes in metabolic parameters were favorable and supportive of the primary weight loss endpoint.

The safety profile of setmelanotide supports approval for weight loss in the intended population. The most common safety issues, including the risk of depression and suicidal ideation, can be addressed in labeling. Although the safety database is exceedingly small, the identified adverse reactions are monitorable. The most common adverse reactions (injection site reactions, hyperpigmentation, and gastrointestinal disorders) are relatively minor. Overall the findings indicate a favorable benefit-risk profile in the indicated population, given the large treatment effect and lack of approved treatments. (b) (4) Labeling should include a stopping rule for patients with *POMC*, *PCSK1*, or *LEPR* variants who do not experience clinically meaningful weight loss. A thorough QT study is required and will be addressed with a postmarketing requirement.

All other review disciplines recommend for approval, including the Office of Pharmaceutical Quality (OPQ), Pharmacology/Toxicology, and Clinical Pharmacology. Pharmacology/Toxicology recommends a post-marketing requirement (PMR) for submission of the final report of a recently completed carcinogenicity study. The Office of Biotechnology Products concluded that the anti-RM-493 ADA assay is not suitable for its intended use and recommends a postmarketing commitment (PMC) to improve setmelanotide confirmatory assay reliability and reproducibility.

A companion diagnostic is under development to identify eligible patients in the labeled population and reduce the likelihood of exposure in patients who are unlikely to benefit. (b) (4) Approval of the companion diagnostic will be a postmarketing commitment.

[1] US Prescribing Information for Contrave (naltrexone and bupropion), Qsymia (phentermine and topiramate extended release), and Belviq (lorcaserin)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Melanocortins are a family of peptide hormones[2] derived from a common precursor, pro-opiomelanocortin (POMC), and include adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), β-MSH, and γ- MSH. • Melanocortins regulate energy homeostasis, hunger, and body weight predominantly via the melanocortin-4 receptor (MC4R) in the hypothalamus. Skin and hair pigmentation are mediated by MC1R expressed on cutaneous melanocytes. • Leptin regulates hunger, satiety, energy expenditure, and body weight, partly via the leptin receptor (LEPR) expressed on POMC neurons in the hypothalamus. • The genetic disorders POMC, PCSK1 and LEPR deficiency are caused by defects in the hypothalamic leptin-melanocortin pathway and are characterized by early-onset extreme hunger and progressive obesity. • POMC Deficiency results from absent or deficient synthesis and processing of neuropeptides due to loss-of-function mutations in the *POMC* gene. Additional phenotypic features may include pale skin and red hair due to decreased MC1R signaling, ACTH deficiency, and adrenal insufficiency. • Loss-of-function mutations in the proprotein convertase subtilisin/kexin type 1 (*PCSK1*) gene result in defective processing of pro-peptides including POMC. Reported features include hyperproinsulinemia, malabsorptive diarrhea, hypogonadotropic hypogonadism, and partial central defects in the adrenal and thyroid axes. • LEPR Deficiency results in impaired signaling upstream of MC4R. Patients may have increased respiratory infections, alterations in immune function, insulin resistance and type 2 diabetes, and delayed puberty due to hypogonadotropic hypogonadism.	POMC, PCSK1 and LEPR deficiency are rare causes of monogenic obesity that result in extreme obesity, severe hunger, progressive weight gain over time, and associated comorbidities.

[2] Yang Y. Structure, function and regulation of the melanocortin receptors. *Eur J Pharmacol*. 2011;660(1):125-130. doi:10.1016/j.ejphar.2010.12.020

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Currently, there is no approved pharmacologic therapy for obesity due to POMC, PCSK1, or LEPR deficiency. • Bariatric surgical approaches such as gastric or intestinal banding or bypass surgery are ineffective in these populations because the extreme hunger of patients with obesity due to POMC, PCSK1, and LEPR deficiency persists post-surgery. • There is no evidence that drugs approved for general obesity would result in weight reduction in these rare cases of monogenic obesity.	There is an unmet need for effective medical therapies for patients with POMC, PCSK1, and LEPR deficiency, as there are no approved treatments. In the absence of therapy, early onset, severe obesity and hyperphagia are expected to result in metabolic disorders, such as type 2 diabetes mellitus, hypertension, dyslipidemia, and CV morbidity and mortality.
Benefit	• In the POMC/PCSK1 trial 80% of subjects (8 out of 10) achieved >10% weight loss at one year of treatment with mean percent decrease from baseline in body weight of 23%. • In the LEPR deficiency population 46% of subjects achieved >10% weight loss at one year of treatment, with a mean 9.7% decrease in body weight. • Most patients with available data experienced reduction in maximal daily hunger scores measured on an 11-point scale. In some patients, withdrawal of study drug during the double-blind period resulted in increased hunger, which decreased when therapy was resumed. Individual responses were highly variable, with some patients experiencing minimal or no changes from baseline. Interpretation of changes in hunger scores was difficult because of the open-label study design and limitations of the patient-reported outcome instrument. • Patients experienced improvements in cardiometabolic parameters, such as waist circumference, blood pressure, lipid profile, and markers of glycemic control.	The application provides substantial evidence of effectiveness of weight loss in the intended population. Results for the primary endpoint and key secondary weight loss endpoint are statistically significant and clinically meaningful. The double-blind withdrawal period provided supportive evidence of the effect of setmelanotide on weight loss in the study populations. Setmelanotide therapy may lead to reduction in hunger in some patients with POMC, PCSK1, or LEPR deficiency. Improvement in cardiometabolic parameters in the study population are supportive of the weight loss endpoints.
Risk and Risk Management	• The most common adverse events with setmelanotide were injection site reactions, skin hyperpigmentation, headache, and gastrointestinal events, such as nausea and vomiting. • Serious adverse events of depression and suicidal ideation occurred in patients treated with setmelanotide. These may be addressed in labeling.	The most common adverse events may be addressed in labeling. Individual patients who do not experience clinically meaningful weight loss will be advised to consider the need for continued therapy. By encouraging discontinuation of the drug in unresponsive patients, the overall benefit-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Sexual adverse events, including spontaneous penile erection in males and disordered sexual arousal and labial hypersensitivity in females, occurred in setmelanotide-treated patients.	risk profile can be improved. A companion diagnostic is required to ensure safe use by identifying the intended population. A thorough QT study is required and will be addressed with a postmarketing requirement.

2. Background

Imcivree (setmelanotide) is a formulation of setmelanotide intended for subcutaneous injection. Setmelanotide is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as an agonist to the human melanocortin-4 receptor (MC4R). MC4R is expressed primarily in the brain, but expression has also been reported in muscle, kidney, and lung.

The melanocortins are a family of peptide hormones derived from a common precursor, pro-opiomelanocortin (POMC), that include adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), β-MSH, and γ- MSH. Melanocortins regulate energy homeostasis, hunger, and body weight, predominantly via MC4R. Setmelanotide is an analog of α-MSH, the endogenous ligand for the MC4R.

According to the applicant, setmelanotide has the potential to restore activity in the MC4R pathway by bypassing defects upstream of the MC4R and directly activating MC4R neurons in the hypothalamus, thereby establishing weight and appetite control in patients with obesity due to genetic syndromes, including POMC, proprotein subtilisin/kexin type-1 (PCSK1), and leptin-receptor (LEPR) deficiency.

POMC deficiency is caused by loss-of-function mutations in the *POMC* gene. Mutations in POMC are very rare in the general population. Null mutations in *POMC* gene lead to hyperphagia, early onset obesity, isolated ACTH deficiency, and hypopigmentation of skin and hair. Heterozygous carriers of null mutations have a significantly higher risk of being obese or overweight.

Mutations in the *PCSK1* gene result in missing MSH neuropeptide synthesis or processing. Congenital deficiency of PCSK1 has been reported in less than 20 unrelated probands (carrying homozygous or compound heterozygous mutations) who presented with malabsorptive diarrhea, failure to thrive during early infancy associated with high mortality rate, severe early-onset obesity, polyphagia, central diabetes insipidus, hypogonadism, hyperproinsulinemia, and other endocrine dysfunctions.

Congenital LEPR deficiency is characterized by severe, early-onset obesity associated with hyperphagia and impaired satiety. Patients are born with a normal birth weight but show rapid weight gain in the first months of life, which results in severe obesity. Additional phenotypic features include frequent respiratory infections, altered immune function, insulin resistance, type 2 diabetes, normal linear growth but reduced adult height, and delayed puberty due to hypogonadotropic hypogonadism.

Currently, there is no approved treatment for POMC, PCSK1, or LEPR deficiency or their manifestations. Severe and early increases in body weight are expected to increase morbidity and mortality due to cardiometabolic risk factors, although life-expectancy is not well characterized because of the extreme rarity of these conditions. There is no evidence that drugs approved for general obesity are effective in this population. Bariatric surgical

approaches are considered ineffective long-term because the extreme hunger in patients with POMC and LEPR deficiency persists post-surgery, resulting in continued excessive food consumption and, in some cases, surgical complications.

Key Regulatory History:

- On October 12, 2011, Rhythm Pharmaceuticals opened IND 112595 to pursue development of RM-493 for treatment of obesity.
- On April 4, 2016, FDA granted Orphan Drug Designation for treatment of POMC-deficiency obesity due to mutations in the POMC gene.
- On Dec 18, 2016, FDA granted Breakthrough Therapy Designation (BTD) for treatment of POMC-deficiency obesity.
- On May 1, 2017, FDA expanded the BTD designation to disorders involving genetic defects upstream of the melanocortin-4 receptor in the leptin-melanocortin pathway
- On August 7, 2019, FDA Granted Rolling Review for the planned New Drug Application.
- On September 27, 2019 FDA held a Type B pre-NDA meeting for Rhythm to obtain guidance and reach agreement on the organization and presentation of data in the application.
- On January 29, 2020, Rhythm submitted a final amended request for Rare Pediatric Disease Priority Review Voucher, to treat children with POMC-deficiency obesity and LEPR-deficiency obesity to the FDA Office of Orphan Products.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval, and I concur with their recommendation. For details of the OPQ quality assessments, refer to the Integrated Quality Assessment authored by the Application Technical Lead, Dr. Muthukumar Ramaswamy, and signed August 25, 2020, and the individual discipline reviews. The following summarizes the key findings.

In his review, Dr. Ramaswamy provided a description of the drug product and drug substance. Imcivree (setmelanotide) injection is (b) (4) solution with pH 5 to 6. The excipients are N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl glycero-3-phosphoethanolamine sodium salt (mPEG-2000-DSPE), carboxymethyl cellulose (CMC), mannitol, phenol, benzyl alcohol, and (b) (4) edetate (b) (4) water for injection.

The proposed commercial formulation is a sterile solution available as a 10 mg/mL multi-dose vial for administration using a (b) (4) syringe. Unopened Imcivree should be stored at 2ºC to 8ºC (36ºF to 46ºF) in the original carton, (b) (4)

The drug substance, setmelanotide acetate, is synthesized by (b) (4) The chemical name is acetyl-L-arginyl-L-cysteinyl-D-alanyl-L-histidinyl-D-phenylalanyl-L-arginyl-L-tryptophanyl-L-

cysteinamide cyclic (2→8)-disulfide acetate. The molecular formula of anhydrous, free base is $C_{49}H_{68}N_{18}O_9S_2$ with a molecular weight of 1117.3 Daltons. Setmelanotide acetate is a white to off-white amorphous powder and is freely soluble in water.

Dr. Joseph Leginus reviewed the chemistry, manufacturing, and control information for the drug substance. He concluded that the drug substance information is adequate to control the identity, purity, strength, and quality of the drug substance used for manufacturing the drug product, and that the proposed drug substance specifications are consistent with batches used in clinical, nonclinical, and registration stability studies. Furthermore, Dr. Leginus concluded that the quality of drug substance produced by each manufacturer (b) (4) is comparable.

Dr. Ted Carver reviewed the drug product information. He concluded that the compatibility of the active ingredient with excipients and the container closure components are supported by drug product stability data, and that the proposed specification is adequate to support the quality of the proposed product. Additionally, he granted the applicant's request for exemption from environmental impact. Dr. Carver also reviewed the container and carton label and found that the information meets regulatory requirements for labeling.

The process reviewer, Dr. Kumar Janoria, concluded that the proposed drug product manufacturing process controls and facility compliance information are adequate to support approval of the NDA. The manufacturing process involves (b) (4)

The microbiology reviewer, Dr. Yan Zheng, reviewed the microbiological controls used in the drug product manufacturing process, including (b) (4) She concluded that the proposed microbiological controls are adequate to support the NDA.

Dr. Ramaswamy concluded that the proposed control strategy is adequate to assure the quality of the product, including limits proposed for individual impurities.

In summary, Dr. Ramaswamy concluded that there are no outstanding deficiencies related to the drug substance, drug product, process/facilities, microbiology, environmental analysis, or container/carton label sections of the NDA. The overall Chemistry, Manufacturing, and Controls (CMC) recommendation is approval.

Office of Biotechnology Products – Immunogenicity Consult Review

The OBP reviewer, Dr. William Hallett, provided recommendations regarding the adequacy of the submitted anti-RM-493 anti-drug antibody (ADA) assay, anti-alpha-MSH antibody assay, anti-RM-493 neutralizing antibody (NAb) assay, and anti-mPEG-DSPE antibody assay. I concur with his recommendations.

Dr. Hallett concluded that the anti-RM-493 ADA assay is not suitable for its intended use, because of intra-assay variability of the confirmatory assay, rendering the results uninterpretable, and that the applicant will need to address the confirmatory assay methods in order to establish reproducibility and interpretability of the ADA data. Dr. Hallett recommends a postmarketing commitment (PMC) to improve the reliability and reproducibility of the setmelanotide confirmatory assay.

Dr. Hallett concluded that the anti-alpha-MSH antibody assay is suitable for its intended use, and that the anti-RM-493 NAb assay is suitable for its intended use for adult samples with less than 10 ng/mL of serum RM-493. The assay was not validated with pediatric serum and results of the NAb assay for pediatric samples will need to be assessed on a case-by-case basis to confirm adequate cut-point establishment.

The applicant has been unable to develop an anti-mPEG-DSPE antibody assay and will no longer pursue its development. Dr. Hallett concluded that because mPEG-DSPE is an excipient, the development of antibodies to PEG will not impact product potency and is low risk.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Shaji Theodore, recommends approval of setmelanotide, with a post-marketing requirement (PMR) for a carcinogenicity study. I concur with his recommendation. Refer to his review signed September 28, 2020 for details. The following summarizes the major findings from Dr. Theodore's review, relevant to approvability and labeling.

Nonclinical pharmacological findings predict a response in genetic forms of obesity with reduced melanocortin production. In vitro, setmelanotide binds to human MC4R and activates the receptor. In mice lacking MC4R function due to gene deletion, setmelanotide produced no pharmacological effects, whereas in rat and monkey models of obesity with intact MC4R function, setmelanotide produced dose-dependent decreases in food intake and body weight. Decreases in body weight in obese mice were associated with decreases in adiposity, and improved glucose tolerance and insulin sensitivity.

Dr. Theodore's summary of safety pharmacology, including off-target effects, was generally reassuring. There were no notable CNS effects in rats at exposures up to 250 times higher than clinically relevant exposures, and no effects on heart rate or blood pressure in safety pharmacology and chronic toxicity studies in monkeys.

Setmelanotide activated human MC1R and MC3R in vitro with 20-fold lower potency compared to MC4R, but had no detectable activity at human MC2R and MC5R. Following chronic dosing, setmelanotide caused a reversible, dose-dependent increase in skin pigmentation in monkeys, without evidence of melanocyte hypertrophy or hyperplasia. Dr. Theodore identified no other potential for off-target effects at clinically relevant doses. There were no abuse-related behavioral changes in nonclinical studies, and abuse potential at higher doses in humans is limited by dose-dependent nausea.

Aside from injection-site reactions, Dr. Theodore identified no important systemic toxicity in chronic toxicity studies, juvenile toxicity studies, or reproductive and developmental toxicity studies.

Severe injection-site reactions associated with a novel excipient, mPEG-DSPE, limited the maximum doses of the setmelanotide clinical formulation to 3 mg/kg/day in rats and 1 mg/kg/day in monkeys (9- and 26-times clinical exposures at the MRHD of 3 mg) in chronic toxicity studies. Setmelanotide formulated in saline was used to allow administration of higher doses of 15 mg/kg/day in rats and 3 mg/kg/day in monkeys (49-times and 38-times MRHD, respectively). The saline formulation also caused injection site reactions, but of less severity.

Juvenile toxicity studies in rats identified no new target organs compared to adults, and no adverse effects on growth, organ development, or behavior at doses up to 15 mg/kg/day setmelanotide in saline and at 3 mg/kg/day with mPEG-DSPE (33- and 7-times the MRHD).

Reproductive toxicity studies in rats and rabbits demonstrated no adverse effects up to the highest dose of 5 mg/kg/day (11-times the MRHD), despite expected, dose-related reductions in maternal food consumption and body weight gain. There were no effects on male fertility in the chronic rat toxicity study. In an embryo-fetal development study of setmelanotide in rabbits, there was no evidence of any adverse effects independent of effects associated with reduced maternal body weight gain.

In a pre- and post-natal development toxicity studies in rats, a dose-dependent decrease in body weight gain and food consumption was observed during the gestation period in maternal animals at clinical exposures, but reproductive performance and pup viability were not affected, and there were no notable adverse findings in the F1 generation at up to the highest dose of 5 mg/kg/day (7-times the MRHD).

Setmelanotide was not genotoxic in standard assays. Dr. Theodore concluded that the weight of evidence indicates minimal carcinogenic concern for setmelanotide in the intended population. A carcinogenicity assessment in a 6-month Tg rasH2 mouse study, and possibly a lifetime rat study (depending on the outcome of the Tg mouse study), will be conducted under a post-marketing requirement (PMR) to assess carcinogenicity.

5. Clinical Pharmacology

The Office of Clinical Pharmacology review team found the clinical pharmacology data submitted acceptable to support approval of the NDA. I concur with their recommendation. Refer to the Office of Clinical Pharmacology review, authored by Dr. Sury Sista, Dr. Eliford Kitabi, and Dr. Katarzyna Drozda, for details of the review.

Dr. Sista was the primary clinical pharmacology reviewer. He concluded that the primary evidence of effectiveness for the proposed dosing regimen from the two pivotal efficacy studies conducted in patients with POMC/PCSK1- and LEPR-deficiency obesity demonstrated

that setmelanotide was effective on the primary endpoint in adults and children 6 years of age and older. The to-be-marketed formulation is the same as the clinical trial formulation that was used in several clinical pharmacology studies and all Phase 3 clinical studies.

Per Dr. Sista's review, setmelanotide should be injected subcutaneously once daily, at the beginning of the day, without regard to the timing of meals, in the abdomen, thigh, or arm, rotating to a different site each day. The drug product should not be administered intravenously or intramuscularly. If a dose is missed, the once daily regimen should be resumed as prescribed with the next scheduled dose.

For adult patients and pediatric patients 12 years of age and older, the recommended starting dose is 2 mg once daily by subcutaneous injection. After 2 weeks, the dose can be increased to 3 mg once daily. If dose escalation is not tolerated, patients may maintain administration of the 2-mg once daily dose.

For pediatric patients ages 6 to 11, the starting dose of IMCIVREE is 1 mg once daily by subcutaneous injection. After 2 weeks, the dose can be increased to 2 mg once daily. If the dose is tolerated and additional weight loss is desired, the dose may be increased to 3 mg once daily. The proposed doses in pediatric populations are supported by population PK and exposure-response analysis.

Dose adjustment of setmelanotide is not required for mild renal impairment. Setmelanotide is not recommended in patients with moderate and severe renal impairment. Setmelanotide was not evaluated in hepatic impairment.

Dr. Sista summarized Absorption, Distribution, Metabolism, and Excretion (ADME). Key issues are summarized here. Following subcutaneous injection, plasma concentrations of setmelanotide reach maximum concentrations at a median Tmax of 8.0 hours after dosing. Steady-state plasma concentrations of setmelanotide are achieved within 2 days, and accumulation over 12 weeks is approximately 30%. Setmelanotide generally exhibits dose proportional PK following multiple-dose subcutaneous administration in the proposed dose range (1-3 mg daily). The mean apparent volume of distribution after SC administration is about 49 L, and the plasma protein binding of setmelanotide is 79.1%. Setmelanotide does not appear to be metabolized by human hepatic microsomes and hepatocytes. Trace amounts of two urine metabolites, M19 and M7, were observed in a small number of subjects. The total apparent steady-state clearance of setmelanotide is about 4.86 L/h. At steady state, approximately 39% of the administered setmelanotide dose is renally eliminated as unchanged drug within 24 hours post-dose.

The mechanism of action outlined in the Clinical Pharmacology review is consistent with the clinical data. The MC4 pathway serves a critical role in the control of food intake and energy balance. Activation of MC4R, the final step in the signaling pathway, decreases appetite and caloric intake, and increases energy expenditure. Under normal conditions, POMC neurons are activated by brain satiety signals, with the hormone leptin acting through LEPR. POMC neurons produce a protein that is specifically processed by the PCSK1 enzyme into melanocyte stimulating hormone, or MSH, the natural ligand, or activator, for MC4R. When

genetic mutations disrupt this pathway, the result is dysregulation of appetite and severe obesity. Setmelanotide targets MC4R, with the putative effect of restoring regulation of food intake and energy balance via the pathway.

Short-term administration of setmelanotide increases resting energy expenditure (REE) and shifts substrate oxidation to fat in obese individuals. Setmelanotide increased mean resting energy expenditure (REE) vs. placebo by 111 kcal/24h (6.4%). Total daily energy expenditure (EE) trended higher while the thermic effect of a test meal and exercise EE did not differ significantly. No adverse effects on heart rate or blood pressure were observed.

Clinical Immunogenicity

Immunogenicity to setmelanotide was evaluated in a majority of the clinical trials in the development program. Of the 79 screening positive samples that were assessed in the confirmatory assay, no samples (0/79) were confirmed positive for antibodies to setmelanotide. As a result, no samples were tested in the neutralizing antibody assay (NAb). There were no observations of a rapid decline in measured setmelanotide concentrations, which would indicate a possible emergence of ADA to setmelanotide. A small number of samples tested positive for antibodies to α-MSH (2.5%), which were present both pre- and post-treatment with setmelanotide. No relationship was found between any ADA parameters assessed (ADA to setmelanotide, neutralizing ADA to setmelanotide, and antibodies to α-MSH) and PK, PD, efficacy, or risk of adverse events with setmelanotide.

Genomics

The Division of Translational and Precision Medicine (DTPM) reviewer, Dr. Katarzyna Drozda reviewed the genetic testing used to select patients for the pivotal studies and the marketed product. The applicant identified (b) (4) as the Rhythm-preferred CLIA-LDT laboratory for post-NDA genetic testing. The American College of Medical Genetics and Genomics (ACMG) guidelines were utilized by (b) (4) for the interpretation of sequence variants and the impact on pathogenicity in the *POMC*, *PCSK1*, and *LEPR* genes, using standard terminology–pathogenic, likely pathogenic, uncertain significance, likely benign, and benign–to describe variants identified in genes that cause Mendelian disorders.

DTPM reviewed the pathogenicity assignment of the genetic variants in the *POMC*, *PCSK1*, and *LEPR* genes submitted and concurs with the applicant's assessment of the pathogenicity of the genetic variants. Because variant pathogenicity is not clearly established for many patients who may benefit from setmelanotide (i.e., patients carrying "variants of unknown significance"), DTPM recommends clinical evaluation and implementation of a stopping rule for management of setmelanotide therapy (i.e., drug discontinuation in patients who do not achieve a threshold weight loss within a specified timeframe). Additionally, DTPM recommends a companion diagnostic to identify eligible patients, to ensure safe use of setmelanotide by reducing exposure in patients unlikely to benefit. DTPM revised the proposed indication to describe the indicated genetic variants for consistency with the enrolled population in the pivotal studies.

Companion Diagnostic

DTPM consistently advised Rhythm during development that it appeared that a companion diagnostic would be necessary to ensure safe and effective use of the drug, consistent with the 2014 FDA Guidance for Industry regarding In Vitro Companion Diagnostic Devices. Although generally the device should be approved concurrently with the New Drug Application, Rhythm had not yet submitted the device application at the time the Mid-Cycle Communication was held on July 22, 2019. At the meeting, the Division clarified that although there are exceptions to concurrent approval as had been discussed at previous meetings between the Agency and Rhythm, exceptions would apply only if the Agency determined during NDA review that the in vitro diagnostic is not necessary for safe and effective use of the product. The Division stated that it did not appear that the exceptions would apply, since the pivotal trials used genetic testing to identify the study population, and genetic testing would be necessary to identify the intended target population for the marketed product.

(b) (4) We have concluded that approval of the device can be completed as part of a postmarketing commitment.

6. Clinical Microbiology

The microbiology reviewer, Dr. Yan Zheng, concluded that the proposed microbiological controls are adequate to support the NDA. For details, refer to Section 3—Product Quality—of this review and the OPQ Integrated Quality Assessment signed August 25, 2020.

7. Clinical/Statistical-Efficacy

The application provides substantial evidence of effectiveness of weight loss in the intended population. The Applicant submitted two clinical studies that each demonstrated clinically meaningful weight loss in patients with obesity due to POMC, PCSK1, or LEPR deficiency. The studies were adequately designed to demonstrate efficacy on the primary endpoint, and the results were statistically robust. (b) (4) .

This section of the review focuses on the major features of the study designs and the methods used to assess the primary and key secondary endpoints regarding their approvability. This section also addresses labeling considerations related to efficacy. For details of the clinical trials and endpoint analyses refer to the FDA Clinical Review authored by Dr. Ovidiu Galescu and the FDA Statistical Review authored by Dr. Jiwei He. Both Dr. Galescu and Dr. He support approval for setmelanotide for a weight-loss indication in the populations evaluated in the studies, and I concur with their conclusions.

Study Design and Methods

The submission consisted of two nearly identically designed phase 3 studies conducted in two populations. Study RM-493-012 (Study 012) enrolled patients with severe obesity phenotype

and biallelic, homozygous or compound heterozygous loss-of-function mutations in the *POMC* or *PCSK1* genes. Study RM-493-015 (Study 015) enrolled patients with severe obesity phenotype and biallelic, homozygous or compound heterozygous loss-of-function mutations in the *LEPR* gene. In both studies, patients with mutations classified as pathogenic, likely pathogenic, or unknown significance using ACMG guidelines were eligible for enrollment, whereas patients with variants classified as likely benign or benign were excluded. Refer to the Genomics subsection within Section 3 (Clinical Pharmacology) of this review, and the DPTM consult by Dr. Drozda for additional details.

Both studies were single-arm, open-label, 1-year studies, consisting of a 2- to 12-week open-able titration period, a 10-week open-label treatment period, an 8-week double-blind, withdrawal period, and a second 32-week open-label treatment period. The primary objective was to demonstrate the effects of setmelanotide on body weight at the end of 1 year of treatment. There was no background lifestyle or behavioral intervention to promote weight loss. Efficacy was evaluated in a protocol-defined pivotal cohort, consisting of those patients who had completed 1 year of evaluation at the time of data cutoff. The Applicant chose the cutoff date with the intent of enrolling approximately 10 patients into the pivotal cohort of each trial. Enrollment remained open in both trials, with additional patients designated as the supplemental cohort.

Only patients who achieved at least 5 kg weight loss (or at least 5% if baseline body weight <100 kg) were to enter the double-blind period, which consisted of 4 weeks on active treatment and 4 weeks of placebo. Patients who did not achieve threshold weight loss during the initial 12 week open-label period could continue open-label setmelanotide for the duration of the studies. Although the protocol conveyed to blinded investigators that the placebo period would be variably timed, by design, every patient who entered the withdrawal period was assigned to the same sequence of 4 weeks setmelanotide followed by 4 weeks placebo.

The Applicant defined two analysis populations to evaluate the primary and key secondary endpoints. The Full Analysis Set (FAS) consisted of all subjects who received at least 1 dose of study medication and had a baseline and at least 1 post-baseline efficacy assessment performed for the primary endpoint. The Designated Use Set (DUS) consisted of subjects who received at least one dose of study drug, experienced ≥5 kg weight loss (or 5% of body weight if <100 kg at baseline) at the end of the initial 10-week open-label period, and proceeded into the double-blind, placebo withdrawal period.

The primary efficacy endpoint was the proportion of patients in the FAS who demonstrated at least 10% weight reduction at approximately 1 year compared to baseline. At a Type C meeting held December 20, 2017, Rhythm had proposed (b) (4) [redacted] The Division disagreed with this proposal, stating in the preliminary comments, (b) (4) [redacted]

(b) (4)

The categorical endpoint represents a compromise position, proposed by the Division in the same communication to preserve statistical power while minimizing the risk of type 1 error despite small samples:

> *"...we find merit in your proposed secondary analysis, which tests whether the proportion of all treated patients who experience at least a 10% reduction in weight is greater than 5% (presuming that the historical data collected in these patients and any natural history data collected confirms that such weight loss is extremely unlikely in the absence of drug). We believe this would be a reasonable primary analysis and our calculations suggest that if you rejected the null hypothesis if at least 3/10 patients had at least 10% weight loss (this corresponds to a 30% proportion of responders, less than your proposed 35% success criteria), you would have roughly 74–95% power to detect true proportions ranging from 35–50% (based on exact binomial calculations)."*

The key secondary endpoints were the percent change from baseline in body weight, the percent change from baseline in weekly average of the daily "most hunger" score in patients 12 years of age and older, and the proportion of patients aged 12 years and older who achieved at least 25% decrease in weekly average "most hunger" score from baseline at approximately 1 year. Other endpoints not controlled for multiplicity included evaluation of changes in markers of glycemia, lipid parameters, waist circumference, assessments of fat mass, and changes in weight and hunger scores during the double-blind withdrawal period. Some of these are discussed within this review as they relate to labeling. Additional exploratory endpoints not discussed in detail in this review include biomarkers such as C-reactive protein, and quality-of-life and health status scores. Refer to the reviews by Drs. Galescu and He, and the clinical outcomes assessment review by Dr. Choudhry for details.

Disposition

Refer to the clinical and statistical review for details of patient disposition. The following summarizes withdrawals and missing data that impact approvability and labeling. In Study 012, one patient discontinued study medication at Week 14 because of lack of efficacy but had available body weight and hunger score data at 1 year. In study 015, one patient discontinued at Week 9 due to an adverse event of Grade 1 eosinophilia, and one patient died due to injuries as a passenger in a motor vehicle accident at Week 33. In addition to these two patients with missing data for all endpoints, one additional patient (3 total) had missing hunger score data at one year. Thus, the FAS consisted of all 10 patients in the pivotal cohort of Study 012 and all 11 patients in the pivotal cohort of Study 015, whereas the DUS considered only 9 patients in Study 012 and 7 patients in Study 015.

Demographics and Baseline Characteristics

Five patients (50%) in Study 012 and eight patients (73%) in Study 015 were female. Most patients in both studies were white and non-Hispanic. Three patients (30%) in Study 012 and one patient (9%) in Study 015 were non-white (Arab, Moroccan, and NA [Study 012], and

South Asian [Study 015]), and one patient in Study 012 was Hispanic or Latino ethnicity. One patient in Study 012 was enrolled in the US, and all others (including all patients in Study 015) were enrolled in other countries (Germany, France, Belgium, Canada, and Spain). Refer to Dr. Galescu's review for additional details.

The median age of patients in the pivotal cohort of Study 012 was 16.5 years of age (range 11 to 30 years), and two patients were less than 12 years of age. Mean baseline BMI was 40.4 kg/m^2 (range 26.2 to 53.3 kg/m^2). Nine patients had mutations in POMC, and one patient had a PCSK1 mutation. In Study 015, the median age in the pivotal cohort was 23.0 years (range 13 to 37 years). Mean BMI was 48.2 kg/m^2 (range 35.8 to 64.6 kg/m^2). All patients had mutations in LEPR.

Although patients in the supplemental cohorts of the two trials did not contribute to the evaluation of efficacy, key demographic and baseline characteristics are presented here for reference, as these patients inform the Safety section of this review. In Study 012, three of the four supplemental patients were male, three patients were non-white (2 Turkish, 1 not reported), and one patient was Hispanic or Latino ethnicity. All four patients were enrolled at non-US sites (Spain, France, Belgium). The median age was 14.5 years (range 10 to 29 years), and 2 patients were less than 12 years of age. Mean baseline BMI was 39.0 kg/m^2 (range 34.4 to 42.7). Three patients had POMC deficiency, and one patient had a (presumed) PCSK1 mutation. In Study 015, both supplemental patients were male, ages 13 and 23, of unknown race and ethnicity, and enrolled in France. BMIs were 42.4 and 69.7 kg/m^2.

Primary Efficacy Endpoint and other Weight-Loss Endpoints

Both the Applicant and the FDA statistical review analyzed the primary endpoint on the FAS in the two pivotal studies. Using the Applicant's analyses, both studies met the primary objective at the predefined level chosen to denote statistical significance. In the FDA Statistical Review, Dr. He also concluded that the two studies achieved the primary objective. Table 1 Summarizes these results.

The applicant calculated a 90% confidence interval (CI) for the proportion of responders using the Clopper-Pearson (exact) method and compared it to a historical response rate. In order to draw statistical inference, a 5% historical control response was assumed (i.e., statistical significance would be met if the lower bound of the CI was larger than 5%). Dr. He agreed that the historical response assumption is reasonable, as the data provided by the Applicant suggest that 0% of POMC or LEPR patients would be expected to experience at least 10% weight loss in one year without intervention. The Applicant's assumption relied on published literature data supplemented by historical data from 24 patients enrolled in the clinical program, demonstrating 6 occurrences of more than 10% weight loss in one year over 315 patient-years of follow up (<2% per patient-year), with 5 of the 6 occurrences following bariatric surgical interventions not allowed during these Study. Dr. He conducted additional analyses, and this review summarizes the differences from the Applicant's approach. For details of statistical methods, refer to the FDA statistical review.

Dr. He concluded that 8 out of 10 (80%, 95% CI: 44.4%, 97.5%) patients with POMC or PCSK1 deficiency in Study 012, and 5 out 11 (45%, 95% CI: 16.8%, 76.6%) patients with LEPR deficiency in Study 015 achieved ≥10% weight loss from baseline at 1 year. Table 1 summarizes these data.

Table 1: Proportion of Patients Achieving at Least 10% Weight Loss at 1 Year (Full Analysis Set)

	Study 012 N=10	**Study 015 N=11**
Number (%)	8 (80)	5 (45.5)[1]
90% CI[2]	(49.3, 96.3)	(20.0, 72.9)
95% CI[2]	(44.4, 97.5)	(16.8, 76.6)
One-sided p-value[3]	<0.0001	0.0001
1. Two subjects with missing value for body weight at 1 year: One patient who discontinued the study early due to AE was considered a non-responder. The other patient who died from injuries following a motor vehicle accident (passenger) considered a responder using linear extrapolation 2. From the Clopper-Pearson (exact) method 3. From exact binomial test, testing the null hypothesis: Proportion =5%.		
Source: FDA Statistical Review, Table 3, p. 10		

There were no missing data for Study 012. For Study 015, the applicant imputed missing values related to study drug as 0 change from baseline, or baseline observation carried forward (BOCF), and imputed missing values unrelated to study drug using linear extrapolation. Dr. He conducted additional sensitivity analyses for Study 015, including a conservative analysis of the primary endpoint considering all patients with missing weight loss data as non-responders. The results of sensitivity analyses did not alter Dr. He's overall conclusions.

The key secondary weight-loss endpoint achieved statistical significance per both the Applicant's and Dr. He's analyses. The Applicant analyzed the key secondary weight-loss endpoint in the DUS population using a linear mixed model whereas Dr. He conducted all analyses on the FAS population using an ANCOVA model.

Per Dr. He's review, mean percent change in body weight from baseline to 1 year was significantly different from 0 in both studies. The estimate of the mean percent reduction in body weight was greater in the Applicant's analysis of the DUS population than in the FDA analysis of the FAS population, because the DUS population excluded patients who did not experience early weight reduction. The effect of setmelanotide on mean changes in body weight was consistent with the findings for the primary endpoint, as mean weight loss appeared to be greater in the POMC/PCSK1-deficiency patients (Study 012) compared to the LEPR-deficiency patients (Study 015). Table 2 summarizes these analyses.

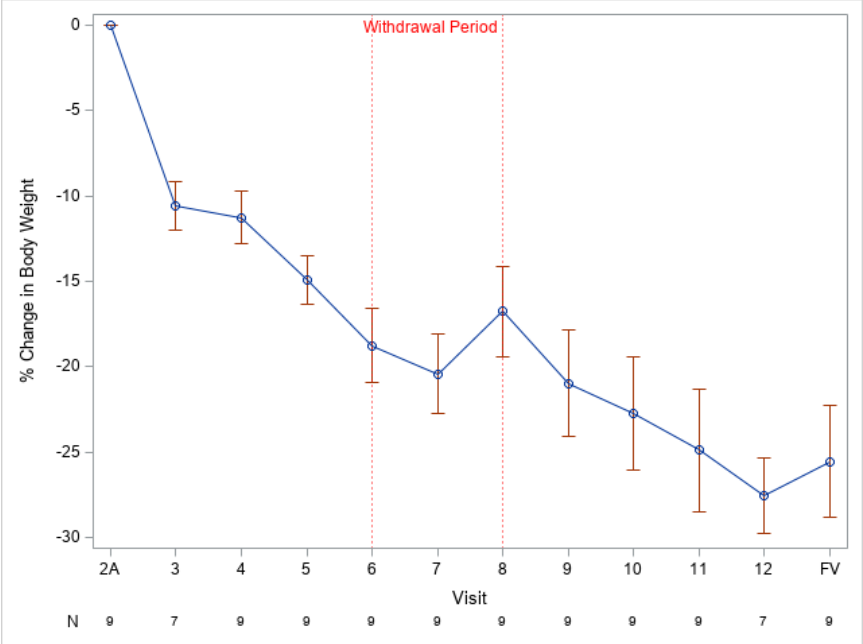
Table 2: Mean Percent Change from Baseline in Body Weight at 1 Year (Full Analysis Set)

	Study 012 N=10	Study 015 N=11
Mean Percent Change (LS Mean)[1]	-23.1	-9.7
95% CI[1]	(-31.9, -14.4)	(-15.7, -4.0)
P-value[2]	<0.0001	0.0005
1. Linear model contains baseline body weight as a covariate. Two subjects in Study 015 with missing body weight at 1 year: one subject with AE imputed as 0 change from baseline. The other subject who died from injuries due to motor vehicle accident (passenger) imputed using multiple imputation and analyzed using Rubin's rule. 2. Testing the null hypothesis: mean percent change=0		
Source: FDA Statistical Review, Table 5, p. 11		

Although there was no parallel control arm in the pivotal studies, Dr. He noted that data from the double-blind withdrawal period provided supportive evidence of the effect of setmelanotide on weight loss in the study populations, as it allowed each subject to serve as their own control. In both studies, patients experienced an increase in body weight after the study drug was withdrawn and a decrease after the study drug was resumed. The results suggested the decrease in body weight was caused by treatment with setmelanotide. Figure 1 and Figure 2 summarize the overall weight trajectories and the changes during placebo treatment. Comparison to historical control data of the populations and the historical data from these subjects provided additional support for the effect of setmelanotide on body weight.

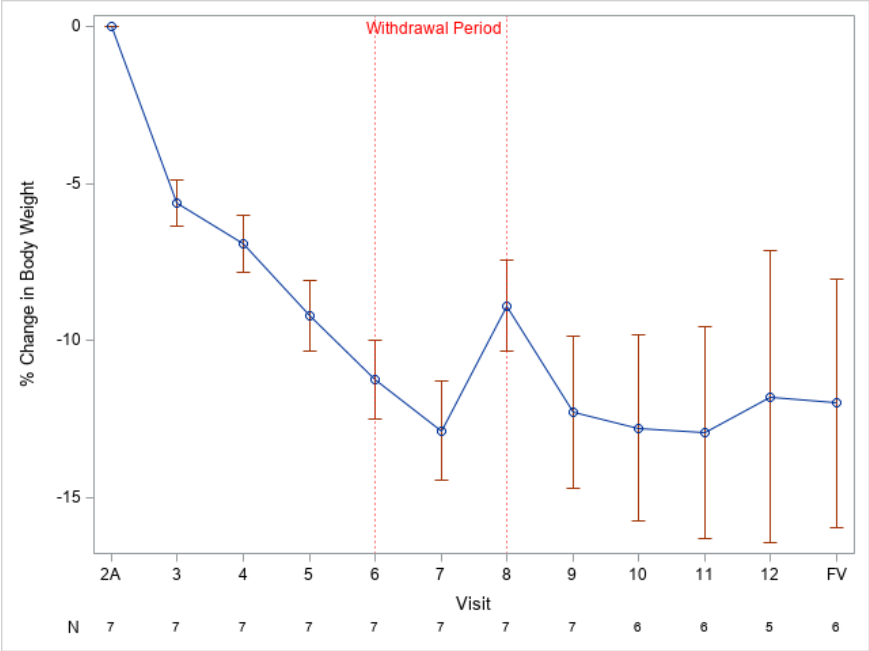
In the clinical review, Dr. Galescu provided a qualitative analysis of weight-loss trajectories for individual patients. Consistently, patients who entered the placebo withdrawal after initially losing weight experienced weight increases followed by weight decreases (or weight stabilization with BMI decrease for growing pediatric patients) when they resumed open-label treatment. There were two notable exceptions in Study 015, both LEPR patients, one adult and one pediatric, who experienced a relatively low magnitude of weight loss early in the study and regained their weight during the second half of the 1-year assessment.

Figure 1: Mean Percent Change from Baseline Body Weight (Designated Use Set) Study RM-492-012



1. Error bars represent standard errors. N represents the number of subjects with observed values.
Source: Statistical Review, Figure 4, p. 14

Figure 2: Mean Percent Change from Baseline Body Weight (Designated Use Set) Study RM-493-015



1. Error bars represent standard errors. N represents the number of subjects with observed values.
Source: Statistical Review, Figure 5, p. 15

In the FDA statistical review, Dr. He concluded that the results from the two studies clearly supported that the drug has an effect in the proposed weight reduction indication. However, because there was no concurrent control in either study, the treatment effect that is attributable to the drug cannot be accurately quantified. Dr. Galescu concurred with this conclusion in the FDA clinical review, stating that the Application provided substantial evidence of effectiveness to support approval, and that the trials demonstrated that weight loss was sustained and significant. I concur with the conclusions of the primary reviewers regarding the efficacy on setmelanotide on weight loss in the study population.

Pediatric Patients – Weight Loss Efficacy

Both studies 012 and 015 included pediatric patients, and the weight loss results for these patients contributed to the primary and secondary weight loss endpoints and supportive data to generally justify inclusion in the indication and labeling. Nevertheless, I reviewed the individual patient profiles to confirm the findings. The individual data inform approvability in the younger age group and the specific labeling recommendations (including dosing and stopping rules). Meaningful weight loss occurred in male and female pediatric patients, including patients younger than 12, among patients with POMC, PCSK1, and LEPR mutations.

In Study 012, four of five pediatric POMC patients (b) (6) achieved the primary endpoint of greater than 10% weight loss from baseline, consistent with the overall results in the trial. Two patients were (b) (6) and the age range at baseline was (b) (6) The fifth patient (b) (6) with PCSK1 mutation, did not achieve the primary endpoint, but experienced a decrease in BMI from 26.6 kg/m^2 to 24.7 kg/m^2 (-7.1%) and BMI z-score (2.66 to 2.09) that would generally be considered clinically meaningful, given his relatively low BMI at baseline. Furthermore, this patient's weight trajectory was confounded by treatment with risperidone from Week 25 until Week 45, because of an episode of depression with suicidal ideation reported on Day 162 during the blinded placebo period. Weight increased during the placebo period and remained essentially unchanged during the subsequent open-label period.

In Study 015, one of three pediatric patients (b) (6), (b) (6) achieved the primary endpoint. A second patient (b) (6) a (b) (6) did not achieve the primary weight endpoint, falling just short of the threshold, but experienced meaningful decreases in weight and BMI, nonetheless. Weight decreased from 115.5 kg at baseline to 104.1 kg at 1 year (-9.9%), BMI decreased from 40.4 kg/m^2 to 35.2 kg/m^2 (13% reduction), and BMI z-score decreased from 3.66 to 3.12. The third pediatric patient (b) (6) did not experience meaningful changes in weight or BMI.

Hunger Scores

(b) (4)

The remainder of this subsection addresses details of the hunger evaluation in the two studies. The key secondary hunger endpoints were (a) mean percent change from baseline in weekly average of maximal daily hunger in patients ≥12 years of age in the DUS population, and (b) the proportion of patients who met the threshold of ≥25% improvement from baseline in hunger (responders) in the FAS population.

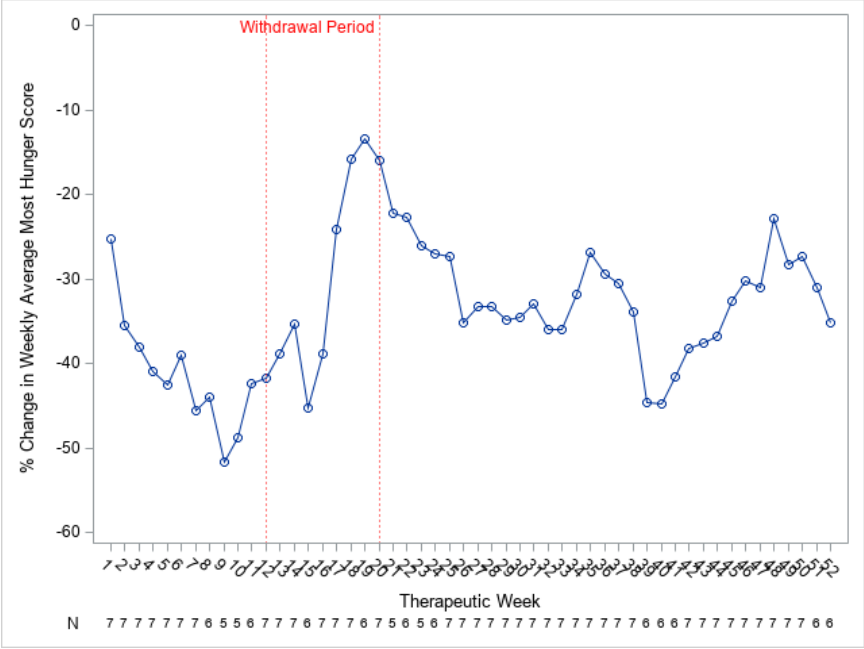
The Applicant utilized a patient-reported outcome (PRO) instrument, Daily Hunger Questionnaire Item 2, which assesses the "most hunger" over a 24-hour period using an 11-point numeric rating scale (NRS) ranging from 0 (Not hungry at all) to 10 (Hungriest possible) as a key secondary endpoint measure in the two phase 3 studies. Hunger scores were assessed in patients ages 12 and older, and changes in hunger score during the double-blind, placebo withdrawal period were available only for patients in the DUS. Hunger data were therefore not available for the two pediatric patients under 12 in Study 012. Additionally, three patients

in Study 015 had missing hunger data at one year: one patient died due to injuries following a motor vehicle accident, and two patients who were excluded from the DUS, including one patient who discontinued due to AE and one patient who experienced lack of efficacy on weight loss.

In Dr. He's analyses in the statistical review, the mean percent change from baseline in the weekly mean of maximal daily hunger, was approximately 31% in patients 12 years of age and older in the FAS of both studies (N=8 in Study 012 and N=11 in Study 015). Dr. He imputed values of zero change for the two non-DUS patients with missing data and used multiple imputation methods and Rubin's rule to impute data for the patient who died. In the categorical analysis, 4 out of 8 patients (50%) in Study 012 achieved 25% reduction in maximal hunger score, and 7 of 11 (64%) patients in Study 015 achieved the threshold per Dr. He's analyses.

The hunger score time profiles suggest that patients who experienced improvement in hunger scores during open-label treatment returned to near-baseline during blinded placebo treatment. While this pattern is illustrative of several patients who experienced changes from baseline in hunger scores, these patients are overrepresented in these data, which exclude missing patients and patients excluded from the DUS. Figure 3 and Figure 4 summarize the hunger score time profiles.

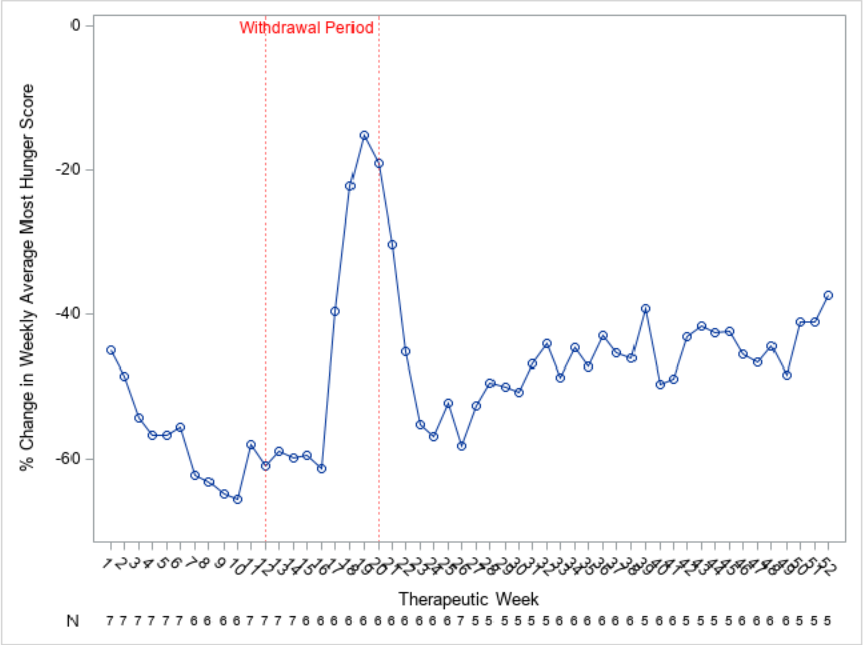
Figure 3: Mean Percent Change in Weekly Average "Most Hunger" Score from Baseline (Designated Use Set, Age ≥12 Years at Baseline) – Study 012



1. N represents the number of subjects with observed values.

Source: FDA Statistical Review, Figure 6, p. 15

Figure 4: Mean Percent Change in Weekly Average "Most Hunger" Score from Baseline (Designated Use Set, Age ≥12 Years at Baseline) – Study 015

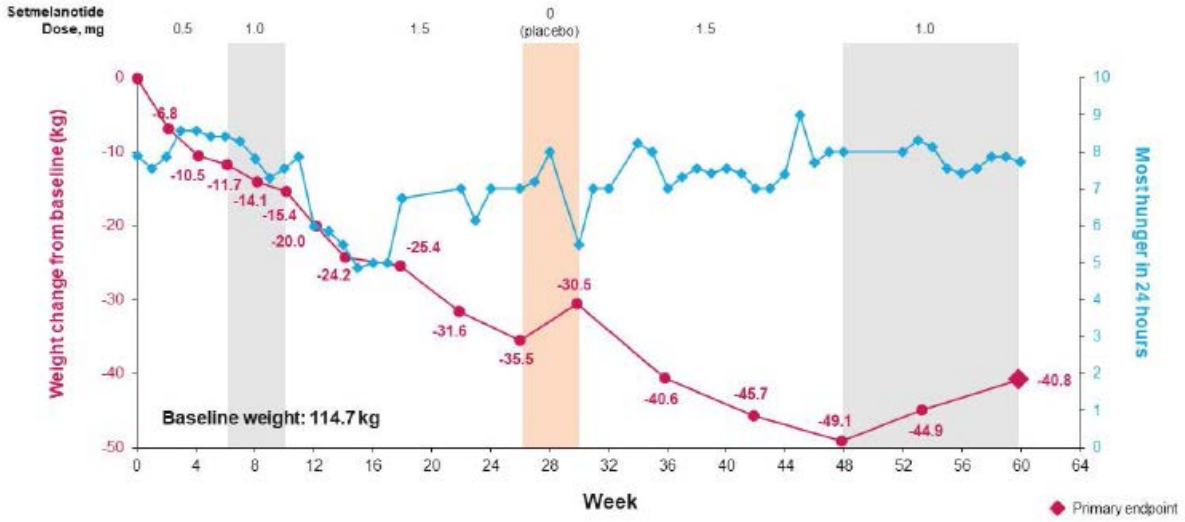


1. N represents the number of subjects with observed values.

Source: FDA Statistical Review, Figure 7, p. 16

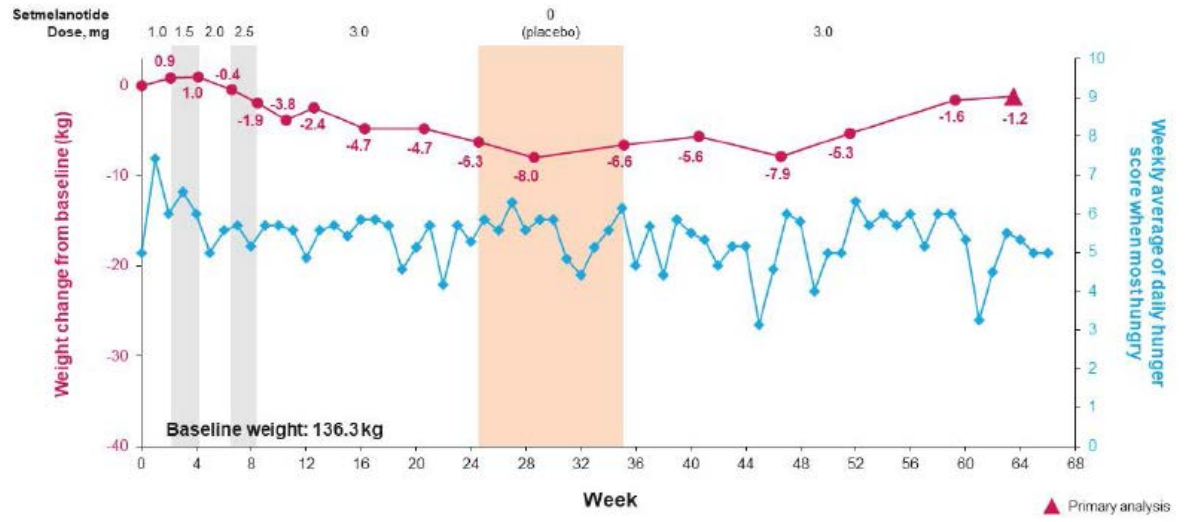
In contrast, the individual patient data presented in Dr. Galescu's review belie considerable between-patient variability. Some patients did not appear to experience substantial changes from baseline in maximal daily hunger scores at any point during the study, such as subject [redacted] (b) (6) (Figure 5) – who nonetheless experienced substantial weight loss (35.6%). Certain patients who experienced decreases in hunger scores >25% associated with substantial weight loss showed some degree of increase in the hunger score during the placebo withdrawal period [redacted] (b) (6) but the scores did not return to near baseline (i.e., the scores remained below the 25% threshold). Both weight responders (such as subjects [redacted] (b) (6) and weight non-responders (such as subjects [redacted] (b) (6) depicted in Figure 6) experienced hunger score excursions above baseline while on treatment. Note that in the applicant's time-profiles, hunger scores are depicted in absolute terms (0-10) whereas weight is shown as change from baseline. For the patient in Figure 5, the baseline hunger score was 7.86, and for the patient in Figure 6, the baseline hunger score was 5.0.

Figure 5: Body Weight (kg) and Weekly Average of Maximal Daily Hunger Score (0-10 Scale) Over Time – Study RM-493-012, Subject (b) (6)



Source: Clinical Study Report, RM-493-012, p. 162 of 272

Figure 6: Body Weight (kg) and Weekly Average of Maximal Daily Hunger Score (0-10 Scale) Over Time – Study RM-493-015, Subject (b) (6)



Source: Clinical Study Report, RM-493-105, p. 239 of 266

The individual patient profiles also indicate that improvement in hunger scores was not entirely consistent with weight loss, a finding also evidenced by relatively low percentage of hunger responders (50%) versus weight loss responders (80%) among POMC patients, and relatively high percentage of hunger responders (64%) versus weight loss responders (46%) among LEPR patients.

During final revisions of the prescribing information, we concluded that a table would communicate the estimated treatment effect, while also representing the variability among patients. We created the following table (Table 3) for placement Section 14.

Table 3: Daily Hunger Scores – Change from Baseline at 1 Year in Subjects Aged ≥12 Years in Study 1 and Study 2 with available hunger data

Parameter	Statistic	Hunger in 24 Hours	
		Study 1 (N=8)	Study 2 (N=8)
Baseline Hunger Score	Median	7.9	7.0
	Min, Max	7.0, 9.1	5.0, 8.4
1-Year Hunger Score	Median	5.5	4.4
	Min, Max	2.5, 8.0	2.1, 8.0
Change from Baseline to 1 Year	Median	-2.0	(b) (4)
	Min, Max	-6.5, -0.1	-4.7, (b) (4)

Note: This analysis includes patients aged 12 years and older who received at least 1 dose of study drug and had available data. Three patients in Study 2 had missing hunger data at Week 52.

Hunger score was captured in a daily diary and was averaged to calculate a weekly score for analysis. Hunger ranged from 0 to 10 on an 11-point scale where 0 = "not hungry at all" and 10 = "hungriest possible."

Source: Reviewer

Dr. He concluded that the lack of a control arm is problematic for making statistical inferences about the hunger score endpoints. (b) (4) .

The COA reviewer, Dr. Yasmin Choudhry, agreed that hunger is a clinically relevant concept for the intended population, and generally supported the approach to symptom assessment but raised questions about the interpretability of the instrument. (b) (4)

Dr. Choudhry also noted that the open-label study design is a limitation of the PRO data that was somewhat mitigated with the use of a double-blind withdrawal period. Additionally, she stated that the small sample size limits the interpretability of the measurement properties of the instrument using anchor-based methods, but she indicated that the qualitative methods used, i.e. cognitive interviews, were informative to determine meaningful within-patient change.

Dr. Choudhry raised concerns that the applicant did not fully assess the impact of migration of the instrument from paper to electronic format. The applicant did not perform usability testing of the electronic device to assess functionality, questionnaire comprehension, and ease of use. Additionally, Dr. Choudhry was concerned that formatting and layout changes of the response scale in the electronic format compared to the original paper format may have influenced subjects' responses.

[redacted] (b) (4) The open-label study design is unable to distinguish the treatment effect from outside influences, while missing data, absence of historical control, and limitations of the PRO instrument limit estimation of a clinically meaningful treatment effect. Nevertheless, the double-blind, placebo withdrawal data suggest that setmelanotide reduces hunger in some POMC, PCSK1, and LEPR patients, and that changes in maximal hunger were associated with weight loss. These findings support inclusion of summary patient data in Section 14 (Clinical Studies) of the Prescribing Information.

Metabolic Endpoints

Changes in metabolic endpoints were generally favorable, associated with weight loss, and supportive of the primary endpoint. Waist circumference is an inexpensive and easily measured indirect estimate of visceral, or intra-abdominal fat, and thus commonly used in the clinical setting. Dual X-ray absorptiometry (DXA) is a more accurate measure of total and visceral fat, and improvements are considered supportive of a primary weight-loss endpoint.

The Applicant reported a mean decrease in fat mass by DXA in the DUS population of approximately 20.3 kg (38.6%) from baseline in Study 012 and 8.6 kg (15.0%) in Study 015. There was no loss of bone density in Study 012 and a small decrease in Study 015, although interpretation was limited by missing data for this variable. Non-bone lean body mass decreased 6.6 kg (10.6%) in Study 012 and 3.9 kg (7.4%) in 5 patients with available data in Study 015. Missing data limited interpretation of bone density and non-bone lean body mass, and the Applicant did not propose including these data in labeling.

The Applicant reported that mean waist circumference decreased from 118.9 cm to 100.5 cm in the DUS population of Study 012 and from 127.3 cm to 114.4 cm in Study 015, but missing data at the final visit limit interpretation of these data. The Applicant also reported trends towards improvement of glycemic parameters, lipid profile, and vital signs. [redacted] (b) (4) in the FAS of Study 012, the Applicant reported mean change from baseline in plasma glucose of -23 mg/dL, and mean change in triglycerides of -37%, not supported by Study 015, and in Study 015, the Applicant reported mean change in LDL-C of -10% and mean change in systolic BP of -4.6 mmHg, both greater than mean changes observed in Study 012. [redacted] (b) (4)

8. Safety

In the FDA clinical review, Dr. Galescu concluded that the safety profile of setmelanotide supports approval for weight loss in the intended population, stating that benefit of therapy in the responder population with obesity due to POMC, PCSK1, and LEPR deficiency outweighs the potential for adverse reactions associated with this compound. The most common safety issues identified in the development programs were injection site reaction, skin hyperpigmentation, gastrointestinal adverse events (nausea, vomiting, abdominal pain), and headache. Adverse events of spontaneous penile erections in males and disturbances in sexual arousal and genital hypersensitivity in females occurred but were mild to moderate in severity and generally self-limited. The most serious adverse events observed in the development were depression and suicidal ideation, and causality of setmelanotide cannot be excluded.

Although the safety database is exceedingly small, the most common adverse reactions are not serious and do not cause significant harm to patients. The more serious adverse reactions are monitorable. The safety database is thus acceptable to support approval in the extremely rare intended population, given the large treatment effect and lack of approved treatments. Such is not the case for other populations. (b) (4)

Because of the limited safety database, Dr. Galescu cautioned that the benefit-risk consideration is favorable only in the indicated population. No risk mitigation strategies are required for approval, but Dr. Galescu supports a stopping rule for patients who do not experience weight loss within 16 weeks of initiating therapy, a concept also endorsed by the DTPM reviewer, Dr. Drozda. A companion diagnostic device is required to identify the intended population and reduce exposure of patients unlikely to benefit. The Division will issue a postmarketing requirement to the applicant to conduct a thorough QT study. I concur with Dr. Galescu on all conclusions regarding safety.

The primary sources of safety data were the pivotal and supplemental cohorts of the two pivotal studies, Study 012 in patients with POMC- or PCSK1-deficiency obesity, and Study 015 in patients with obesity due to mutations in LEPR. There were no placebo-controlled trials in the intended populations, and most of the placebo-controlled data in other populations evaluated lower doses that are not applicable to these indications. Supportive safety data comes from a single randomized, placebo-controlled trial in healthy obese patients, Cohort C of Study RM-493-009 (Study 009).

The primary safety data are derived from 27 patients in Studies 012 and 015 followed for at least one year. Dr. Galescu did not identify any issues with data integrity or submission quality. He found the Applicant's approach to recording, coding, and categorizing adverse events to be reasonable and appropriate.

Deaths

There was one death in Study 015, subject (b) (6), a (b) (6) with LEPR-deficiency obesity who died due to injuries sustained as a passenger in an automobile accident at Week 33.

Serious Adverse Events

Overall, there were 13 serious adverse events (SAEs) in 10 patients. Each SAE Preferred Term (PT) occurred in only one patient, except depression occurred in 2 patients and suicidal ideation occurred in a patient who also experienced depression (not classified as an SAE). Most other SAEs were either events consistent with the study population (adrenocortical insufficiency, cholecystitis, pneumonia, gastric banding reversal) or accidents (road traffic accident) not clearly attributable to study drug.

Withdrawals

No patients withdrew due to AE in Study 012. One patient, Subject (b) (6) withdrew from Study 015 due to Grade 1 eosinophilia assessed as probably related to study medication. Another patient, Subject (b) (6), noted above, died in a motor vehicle accident.

Treatment Emergent Adverse Events

The most frequent treatment emergent adverse events (TEAE) were injection site reactions, skin hyperpigmentation, and gastrointestinal disorders (Table 4). The adverse events are notable for depression, spontaneous penile erections in males, and alopecia.

Table 4: Treatment Emergent Adverse Events by Preferred Term in Order of Frequency Occurring in >10% of Patients (Safety Population) – Study 012 and 015, Pivotal and Supplemental Cohorts

Preferred Term	N=27	Percent (%)
Injection site reaction[a]	26	96
Skin hyperpigmentation[b]	21	78
Nausea	15	56
Headache	11	41
Diarrhea	10	37
Abdominal pain[c]	9	33
Back pain	9	33
Fatigue	8	30
Vomiting	8	30
Depression[d]	7	26
Upper respiratory tract infection	7	26
Spontaneous penile erection[e]	3	23
Arthralgia	5	19
Asthenia	5	19
Dizziness	4	15
Dry mouth	4	15
Dry skin	4	15
Insomnia	4	15
Vertigo	4	15
Alopecia	3	11
Chills	3	11
Constipation	3	11
Influenza-like illness	3	11
Muscle spasm	3	11

Preferred Term	N=27	Percent (%)
Pain in extremity	3	11
Rash	3	11
Suicidal ideation	3	11
[a] Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration [b] Includes skin hyperpigmentation, pigmentation disorders, skin discoloration [c] Includes abdominal pain and upper abdominal pain [d] Includes depressed mood [e] n = 13 male patients		
Source: FDA Clinical Reviewer		

Supportive Safety Data

Study 009, titled "A Staged, Phase 1b/Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of RM-493, a Melanocortin 4 Receptor (MC4R) Agonist in Obese Patients using a Once or Twice Daily Subcutaneous Injection Formula" consisted of three sequential stages, in otherwise healthy, obese patients with BMI between 30-40 kg/m^2. The study consisted of three sequential stages, including Stage C, a randomized, controlled trial in patients randomized to setmelanotide 2 mg daily or matching placebo for 12 weeks of treatment. Dr. Galescu analyzed TEAEs in this trial because it represents the only controlled data with similar dose exposure to pivotal studies.

Notably, TEAEs in Study 009 were similar in character and frequency to those in Studies 012 and 015, despite a substantially shorter treatment duration. Depression occurred more frequently with setmelanotide than placebo (zero events), suggesting that events in the pivotal studies may not represent background risk in the population. Sexual adverse events occurred more frequently with setmelanotide than with placebo in both men and women, and alopecia occurred more frequently than placebo, suggesting a drug-associated effect independent of weight loss. Table 5 Summarizes these data.

Table 5: Adverse Reactions Occurring in 5% or More Patients Treated with Setmelanotide and More Frequently than in Placebo (Safety Population) – RM-493-009

Adverse Reaction	Setmelanotide N=59 (%)	Placebo N=40 (%)
Skin Hyperpigmentation	47 (80)	3 (8)
Injection Site Reactions	42 (71)	15 (30)
Nausea	32 (54)	5 (13)
Headache	29 (50)	11 (28)
Vomiting	18 (31)	4 (10)
Spontaneous Penile Erection	9 (38)[a]	0
Diarrhea	16 (27)	4 (10)
Fatigue	13 (22)	3 (8)
Abdominal Pain	10 (17)	2 (5)
Back Pain	8 (14)	0
Disturbance in Sexual Arousal	5 (14)[b]	0

Adverse Reaction	Setmelanotide N=59 (%)	Placebo N=40 (%)
Sleep Disorder	7 (12)	0
Melanocytic Nevus	4 (7)	0
Alopecia	4 (7)	0
Depression	3 (5)	0
[a] Male subjects, N=24 [b] Female subjects, N=35		
Source: Clinical Reviewer		

The Applicant assessed all events of depression or suicidal ideation as either unrelated or unlikely related to study drug, including the three events categorized as SAEs. The Applicant included depression and suicidal ideation in Section 5 (Warnings and Precautions) (b) (4) [redacted] Dr. Galescu recommended strengthening the warning language, and I concur.

Laboratory

There were no clinically meaningful changes of shifts in clinical laboratory assessments. Refer to the clinical review for details.

Vital Signs

There were no increases in office blood pressure or heart rate. Refer to the clinical review for details.

ABPM

There were no concerning trends or shifts in ambulatory or office blood pressure monitoring in the clinical program. The evaluation is adequate for this rare population, but if the applicant seeks approval for a broader population, a dedicated ABPM study may be required.

The applicant reported that there were no signals of blood pressure or heart rate increases in 24-hour Ambulatory Blood Pressure Monitoring (ABPM) conducted during the Phase 1 and 2 clinical trials (RM-493-002, RM-493-003, and RM-493-009) at doses up to 25 mg/kg/day.

Additionally, the applicant reported that there were no differences from baseline or trends for increase in blood pressure or heart rate in pooled data evaluating from the two phase 3 Studies, 012 and 015, and the phase 2 Study RM-493-014. Trends in ABPM indicated a decrease from baseline blood pressure with setmelanotide. Office blood pressure data did not demonstrate any trends for increase in blood pressure, but the upper bounds of the 95% confidence intervals were +5 mmHg for systolic and +2 mmHg for diastolic blood pressure.

In his review, Dr. Galescu showed time profiles of blood pressure and heart rate data in Studies 012 and 015. Mean blood pressures remained stable or trended down during dose titration and over the course of the study. Individual blood pressure-time profiles demonstrated considerable within-patient variability but did not reveal any outliers with overall trends towards increases in blood pressure or heart rate.

I additionally reviewed individual blood pressure trends and shifts from baseline among the patients in the two phase 3 studies. Changes were generally consistent with the mean changes described above. Overall, 9 of 21 patients in the studies experienced increases in systolic blood pressure and 11 or 21 patients experienced increase in diastolic blood pressure. The changes were generally small in magnitude (3-9 mmHg systolic and 1-5 mmHg diastolic for most patients). One patient (b) (6) experienced an increase from 134/72 mmHg at baseline to 145/73 at the final visit. One patient (b) (6) experienced an increase in diastolic blood pressure of over 10 mmHg, from 119/61 mmHg to 123/72 mmHg. Four patients shifted two a lower BP category, while two patients shifted to a higher category. Table 6 summarizes blood pressure shifts.

Table 6: Blood Pressure Shifts from Baseline to Last Visit – Studies RM-493-012 and RM-493-105, Full Analysis Set, Pivotal Cohort

	Last Visit			
Baseline	**Normal**	**Elevated**	**Stage 1**	**Stage 2**
Normal	11	1	0	0
Elevated	3	1	0	0
Stage 1	1	0	3	1
Stage 2	0	0	0	0
Normal = <120/80 mmHg Elevated = SBP 120-129 and DBP <80 mmHg Stage 1 = SBP 130-139 or DBP 80-89 mmHg Stage 2 = SBP > 140 or DBP >90 mmHg				

Source: Reviewer

QT

The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies consult review by Dr. Garnett concluded that a thorough QT study is necessary to evaluate the arrhythmogenic potential for setmelanotide. Dr. Garnett concluded that the Applicant's QT report of pooled data from 57 patients across different trials did not provide adequate quality or exposure margin. I concur with the recommendation. The Division will issue a post-marketing requirement to the Applicant to conduct a thorough QT study to evaluate the effect of setmelanotide on the QTc interval.

In conclusion, the safety profile of setmelanotide supports approval for weight loss in the intended population. The most common safety issues, including risk of depression and suicidal ideation, will be addressed in labeling. A companion diagnostic is required to ensure safe use by identifying the intended population. Labeling should include a stopping rule for patients who do not experience clinically meaningful weight loss, which will improve the benefit-risk profile for individual patients, i.e., patients who do not derive benefit can

discontinue the drug. A thorough QT study is required and will be addressed with a postmarketing requirement.

9. Advisory Committee Meeting

No Advisory Committee meeting was conducted for this application. The Applicant and FDA had previously reached agreement on the key design elements of the pivotal efficacy studies. During review of the application, no concerns arose regarding the validity or clinical meaningfulness of the weight-loss results, and the review identified no new safety issues that might impact the benefit-risk consideration requiring Advisory Committee input.

10. Pediatrics

FDA granted setmelanotide Orphan Designation for POMC deficiency (including PCSK1) and LEPR. The application is exempt from Pediatric Research Equity Act (PREA) requirements.

Pediatric data supporting indications for pediatric patients ages 6-11 and pediatric patients aged 12 and older are discussed in the Efficacy Section of this review.

Dr. Jacquline Yancy provided a consult review for the Division of Pediatrics and Maternal Health (DPMH) regarding the clinical components of labeling related to pregnancy and lactation. The following summarizes her key conclusions incorporated into final labeling.

(b) (4)

Because the formulation includes benzyl alcohol and there is potential fetal exposure, DPMH recommended stating that setmelanotide is not recommended for use during pregnancy. Dr. Yancy's review further recommended consideration of a drug utilization review in the first three years after approval to consider the feasibility of a postmarketing requirement study to evaluate use of setmelanotide in females of reproductive potential and pregnancy and infant outcomes.

The animal pre/post-natal developmental study shows that setmelanotide is excreted at low levels in the milk of rats, but no quantifiable setmelanotide concentration was found in the plasma of nursing rat pups, suggesting that the drug may not be absorbed from the gastrointestinal tract. Although benzyl alcohol is rapidly metabolized by the lactating mother, DPMH considered the risk exposure to the breastfed infant to be low. Nevertheless, because adverse reactions have occurred in premature neonates and low birth weight infants who received intravenously administered benzyl alcohol-containing drugs, DPMH added a recommendation not to breastfeed to the draft labeling.

Because animal data do not indicate an adverse effect from setmelanotide on fertility, because there are no clinical data regarding its effects on human fertility, and because there is no

evidence of teratogenicity, the DPMH review recommends omission of Section 8.3 from labeling. I concur with Dr. Yancy's recommendations for labeling.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) conducted investigations of two clinical sites in addition to the sponsor and concluded that the inspectional findings support validity of the data reported by the sponsor. I concur with the conclusion. Refer to the Clinical Inspection Summary authored by Dr. Kleppinger and signed October 8, 2020, for details.

The initial inspection assignment issued on April 10, 2020 planned to conduct good clinical practice (GCP) inspections of five clinical investigator sites and the sponsor, covering Studies RM493-012, RM493-015, (b) (4). Studies 012 and 015 are pertinent to the indication. (b) (4)

The inspection of Dr. James Swain/Scottsdale, AZ (Site 006, Study RM493-102) demonstrated adequate adherence to the regulations and the investigational plan, and no objectionable conditions. (b) (4) Inspection of the sponsor, Rhythm Pharmaceutical, Inc. Boston, MA revealed adequate adherence to the regulations and the investigational plan and no objectionable conditions.

The ongoing COVID-19 global pandemic limited the ability of the Office of Regulatory Affairs (ORA) to conduct onsite foreign GCP inspections. As a result, inspections of Dr. Allison Bahm/Canada (Site 004, Study RM493-012), Dr. Karine Clement/France (Site 002, Study RM493-015), and Dr. Peter Kuehnen/Germany (Site 001, Study RM493-012) were not conducted. Remote data investigation of source records by ORA was not feasible due to local restrictions.

Financial disclosures:

No investigators or sub investigators (study investigators) in RM-493-012 or RM0493-015 met the criteria for Financial Interest in the study. The Applicant submitted Financial Form 3454 to the NDA.

12. Labeling

Prescribing Information

- INDICATIONS AND USAGE section:
  - The applicant proposed an indication for the treatment of obesity [redacted] in the intended population. We revised the indication to chronic weight management in patients with obesity due to POMC, PCSK1, and LEPR deficiency for consistency with other weight-loss products, and the inclusion criteria and primary endpoints (change from baseline in weight) of the pivotal studies.
  - Added language that the obesity syndromes that comprise the intended population must be confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).
  - Added Limitation of Use stating that IMCIVREE is not indicated in patients with other conditions in whom the drug is not expected to be effective, including patients with obesity due to suspected POMC, PCSK1, or LEPR deficiency with genetic variants in the genes classified as benign or likely benign, in other genetic syndromes, or general (polygenic) obesity.
- DOSAGE AND ADMINISTRATION section:
  - Clarified patient selection criteria genetically confirmed or suspected deficiency of POMC, PCSK1, or LEPR, and patients with variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)
  - Advised that currently available tests for the detection of variants in the *POMC*, *PCSK1*, or *LEPR* genes have not been approved or cleared by the FDA
  - Edited dose titration for clarity and consistency with current labeling practices. Removed [redacted] replaced with bulleted format. Combined starting dose and titration instructions for adults and pediatric patients aged 12 and older.
  - Edited administration section for clarity and consistency with current labeling practices, including bulleted list.
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - Removed [redacted]
  - Rearranged Warnings (5.1 Disturbance in Sexual Arousal, 5.2 Depression and Suicidal Ideation, 5.3 Skin Pigmentation and Darkening of pre-existing Nevi)
  - For all warnings added data from clinical studies informing the risk
  - Added warning for general risk of benzyl alcohol preservative in infants and neonates
  - Adverse events: Revised tables to include all common AEs observed regardless of causality assessment, based on supportive information from randomized data in another population. Added information regarding disorders of sexual arousal and labial hypersensitivity in females. Revised immunogenicity section
- CLINICAL STUDIES
  - Extensive revisions to study descriptions
  - Edited Tables depicting primary and key secondary weight-loss endpoints

- Substantial revision to hunger data, including (b) (4)
  summarized double-blind withdrawal briefly, (b) (4)
- Removed (b) (4)

Other Labeling
The review team, with guidance from the Division of Medical Policy Programs and the Office of Prescription Drug Promotions, made changes to the Patient Information and Instructions for Use, consistent with the Prescribing Information and current practices.

13. Postmarketing

No Postmarketing Risk Evaluation and Mitigation Strategies (REMS) are required for approval of this application.

Final agreed Postmarketing Requirements and Commitments

Postmarketing Requirements

1) Complete the ongoing 26-week carcinogenicity study of setmelanotide in transgenic Tg.rasH2 mice

   Final Report Submission: January 2021

2) Conduct a thorough QT trial to evaluate the effect of setmelanotide on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non- Antiarrhythmic Drugs, and its Questions and Answers (R3).

   Draft Protocol Submission: March 2021
   Final Protocol Submission: October 2021
   Trial Completion: June 2022
   Final Report Submission: December 2022

Postmarketing Commitments:

3) Improve the performance and repeatability of the setmelanotide confirmatory ADA assay to ensure that the confirmatory ADA assay can reliably test for the presence of ADA in clinical samples.

   Study Completion: July 2021
   Final Report Submission: September 2021

4) Conduct adequate analytical and clinical validation testing to establish an in-vitro diagnostic device developed to accurately and reliably detect patients with variants in the POMC, PCSK1, and LEPR genes that may benefit from setmelanotide therapy. The clinical validation should be supported by a clinical bridging study comparing the in-vitro diagnostic device and the clinical trial enrollment assays.

Final Report Submission: November 2020

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
11/25/2020 03:12:59 PM

ELLIS F UNGER
11/25/2020 05:31:40 PM
I agree with the assessments, commentary, and conclusions of Dr. Sharretts, supporting the approval of this application.